Remarks

In the December 13 Action, the Examiner acknowledged a previous restriction requirement and Applicant's election of claims 9-15. The remaining claims i.e., claims 1-8 and 16-19, have been withdrawn from prosecution. Applicant reserves the right to pursue prosecution of those claims in one or more subsequent applications.

With respect to the pending claims, the Examiner rejected claims 9-13 and 15 under § 103 as being obvious based upon U.S. Patent 4,117,161 to Pozuelo and U.S. Patent 3,819,635 to Pachter et al.

The Examiner also rejected claims 9-15 under § 103 as being obvious over the '161 patent to Pozuelo, the '635 patent to Pachter et al., and further in view of U.S. Patent 5,789,411 to Gooberman et al. and/or U.S. Patent 5,760,044 to Archer.

In view of the following explanations as to the significant differences between the pending claims and the cited art, it is respectfully submitted that the rejections must be withdrawn, and claims 9-15 allowed.

A. The Methods Recited in the Claims at Issue

Claims 9-15 are directed to the combined use of AMPT and Haloperidol. The recited methods, when employed for treating a variety of addictions, abolish craving and withdrawal symptoms otherwise arising as a result of the addiction. Typically, craving and withdrawal symptoms are eliminated in only 6 to 8 hours after the present invention treatment methods. These methods provide a significant improvement and advance over Applicant's previous U.S. Patent 4,117,161. These claimed methods provide an improved and more efficient treatment strategy, thereby reducing the costs of the treatment and lessening the suffering of the patient.

Another advantage of the methods of the pending claims is that the treatment can be started immediately, once the results of blood and urine analysis are known, regardless of the state of intoxication of the patient. That is, treatment with AMPT and Haloperidol can be started immediately, without the need for the patient to continue taking the addictive drug. This is in contrast to Applicant's previous treatment method utilizing only AMPT. That previous treatment approach required the use of some oral medication, usually Methadone, to placate the craving and signs of withdrawal until the AMPT started to show its efficacy, which is typically, 2 to 3 days.

No reference is made in Applicant's '161 patent about the combined use of AMPT and Haloperidol, the increased efficiency of treatment regimes using that combination of agents, and the wide array of addictions which may be treated using this unique combination of agents. The methods recited in independent claims 9 and 15 are based on a new discovery, relating to the biochemistry of addiction and bipolar illness and the use of Haloperidol in conjunction with AMPT. The combined use of AMPT and Haloperidol was not disclosed or even suggested in Applicant's previous '161 patent. Also, in none of the patents to Pachter, Gooberman, or Archer, is there any mention about the combination of AMPT and Haloperidol or the efficacy of that combination on various addictions. Furthermore, in none of these cited patents (Pachter, Gooberman, Archer) is disclosed tyrosine-hydroxylase, D2 dopamine, Dopamine -β-hydroxylase or any biochemical bases that would provide a basis or suggestion for the combination of AMPT and Haloperidol. These aspects are explained in greater detail below.

B. The Rejection of Claims 9-13 and 15 Under § 103 Based upon U.S. Patents 4,117,161 to Pozuelo and 3,819,635 to Pachter et al. Must Be Withdrawn

In support of this ground of rejection, the Examiner asserted:

> The present claims (e.g. claims 9-13 and 15) are directed to a method of treating narcotic addiction (e.g. addiction to heroin or cocaine or amphetamines or marijuana) by administering:
> I. alpha-methyl-para tyrosine (AMPT) and
> II. 4-[4-(p-chlorophenyl)-4-hydroxy-piperidino]-4'-fluorobuyrophenone (HALDOL or HALOPERIDOL).
>
> Pozuelo teaches the use of AMPT to treat narcotic (e.g. morphine, marijuana etc.) and/or amphetamine addiction by treating the craving and withdrawal symptoms when a patient is deprived of such narcotics and/or amphetamines. Pozuelo further teaches AMPT amounts (e.g. see patent claims) within the presently claimed scope, while further teaching that the "[T]he exact amount to be utilized varies from person to person depending on the degree of addiction and is determined empirically". See e.g. col. 2, especially lines 19-30.
>
> The Pozuelo reference differs from the presently claimed invention by failing to further utilize HALOPERIDOL.
>
> However, Pachter et al. teach that "[I]t has been reported in the literature that...HALOPERIDOL...has found some experimental use in the alleviation of narcotic addiction withdrawal symptoms" and it is therefore preferred to combine HALOPERIDOL with narcotic antagonists (such as the Pachter et al. Reference 14-Hydroxymorphinan derivatives which are analogous in structure to NALTREXONE: e.g. see formulas in col. 4; and Table 5 reference to "NALOXONE") in order to produce a product preventing narcotic abuse and providing supportive therapy in the absence of opiates. See Pachter et al. Col. 16, especially lines 2-15. The Pachter

> reference teaches HALOPERIDOL oral administration of 0.5-5 mg two or three times daily (e.g. col. 16, lines 15-20).
>
> To the extent that the Pachter reference dosage differs from the HALOPERIDOL dosage presently claimed, in combination with AMPT, it is noted that the exact amount of HALOPERIDOL to be utilized in a combined formulation would vary from person to person depending on the degree of addiction and is determined empirically (e.g. see Pozuelo at col. 2, especially lines 19-30) and thus optimum dosage would be obvious to determine by a medical practitioner.
>
> Accordingly, one of ordinary skill in the art at the time of applicant's invention would have been motivated to administer Pozuelo's AMPT composition with Pachter's HALOPERIDOL composition, since both treat narcotic addiction (e.g. address narcotic withdrawal symptoms); and in order to obtain the combined additive effect of each of the drugs taken separately.
>
> Courts have determined that it is indeed obvious to one of ordinary skill in the art to co-administer two (or more) pharmaceuticals, each of which is taught to have the same utility, when they are individually known to have that utility, absent unexpected results. See e.g. *In re Kerhoven,* 626 F.2d 846,205 USPQ 1069 (CCPA 1980).
>
> Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to formulate dually administer AMPT and HALOPERIDOL for treating narcotic addiction as presently claimed.

Page 3-5 of the December 13 Action.

It is respectfully submitted that this rejection is misplaced and must be withdrawn. There is no teaching or suggestion in either of the '161 patent to Pozuelo or the '635 patent to Pachter et al. to combine the administration of AMPT and Haloperidol (or Haldol) for the treatment of narcotic addition. That is, neither of the patents cited by the Examiner teaches the combination or joint administration of AMPT with Haldol or Haloperidol.

It is acknowledged that the '161 patent describes treatment regimes utilizing AMPT.

As to the previous use of Haloperidol, the Examiner correctly notes that, that agent has been well known for many years.

However, the claims at issue recite the joint administration of these agents. That is, the presently claimed methods are directed to the combined use of these agents in various treatment regimes. The present application contains extensive discussion as to the unexpected advantages of the combined use of AMPT and Haloperidol, and furthermore, discloses the significant advantages of this combination over the sole use of AMPT. Specifically, the significant and unexpected advantages of employing the presently claimed combination of AMPT and Haloperidol, over the use of AMPT alone, are described in detail on pages 9-10 of the application.

Applicant's attorneys acknowledge the Examiner's grounds for the rejection. However, under the Examiner's standard of review, nearly all new pharmaceutical formulations would be ineligible for patent protection since most formulations contain previously known agents.

Instead, the standard of review as to the patentability of the pending claims is whether the cited prior art provides any teaching for the claimed methods. This involves determining whether the cited art teaches the recited joint use and combination of AMPT in conjunction with Haloperidol. It is respectfully urged that the cited art fails to provide the requisite teaching necessary to properly support a rejection under § 103.

The entire focus of the '161 patent is to use AMPT and an alkalinizing agent in a treatment regime. There is absolutely no teaching or even a suggestion of combining AMPT with another treatment agent.

As to the '635 patent to Pachter et al., if one followed the teachings of that patent, one would be motivated to combine Haloperidol with a class of narcotic antagonists that are entirely different than AMPT. Specifically, Pachter et al. instruct that Haloperidol be combined with 1-3,14-dihydroxy-6-cyclopropyl-methylmorphinan. There is absolutely no teaching or even a suggestion of, combining Haloperidol with AMPT.

The present rejection is based on impermissible hindsight reconstruction that it is obvious to combine the use of AMPT and Haloperidol. This conclusion is only reached by using the present application and pending claims to provide the "link" between jointly administering AMPT and Haloperidol. Without the knowledge gained from the present application and claims, there is no teaching or suggestion in the art, and particularly in either of the cited '161 or '635 patents, to employ the combination of AMPT and Haloperidol. The Federal Circuit has clearly prohibited the use of hindsight reconstruction in § 103 rejections. "Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the...invention." *ATD Corp. v. Lydall, Inc.,* 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998). "Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." *Para-Ordnance Man., Inc.*

v. SGS Importers Int'l., Inc., 73 F.3d 1085, 37 USPQ2d 1237 (Fed. Cir. 1995), *cert denied*, 519 US 822 (1996).

Moreover, if one followed the teachings of either or both of these patents, one would be directed away from the subject matter of the claims under review. If one followed the teachings of the '161 patent, one would be motivated to use AMPT as the sole active agent in a treatment regime. One would not be motivated by the '161 patent to identify another agent for jointly administering with AMPT. And, if one followed the teachings of the '635 patent, one would be motivated to use Haloperidol in conjunction with a specific type of 14-hydroxymorphinan derivative.[1] That is, the '635 patent teaches directly away from the subject matter of the claims at issue. The pending claims do not recite the use of 14-hydroxymorphinan derivatives. The teachings of the '635 patent cannot be ignored. Nor is it permissible to selectively pick and choose among the various passages of the '635 patent so as to rely upon some and conveniently ignore others.

The Federal Circuit recently explained that "as a 'useful general rule'...references that teach away cannot serve to create a *prima facie* case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 60 USPQ2d 1001 (Fed. Cir. 2001).

In support of the rejection, the Examiner cited *In re Frederik Johan Kerkhoven,* 626 F.2d 846, 205 USPQ 1069 (CCPA 1980) for the general proposition that "it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose." However, a careful reading of that opinion reveals that that decision is very distinguishable from the present matter.

First, the invention at issue in *Kerkhoven* related to the production of particulate detergent compositions. Specifically, the claimed method which was held to be obvious involved steps of forming slurries, drying them, and then mixing them. These basic processing operations were fully disclosed in the prior art and the separate disclosures were readily combinable.

In contrast, the methods of the present application at issue pertain to methods for treating addiction or a certain psychosis by the joint administration of two

[1] As will be appreciated, N-substituted-14-hydroxy-3-substituted-morphinan derivatives are chemically, structurally, and empirically very different from alpha-methyl-para-tyrosine (AMPT).

pharmaceutical agents. The fields of pharmacology and medicinal psychiatry are dramatically different from that of making detergent compositions. Moreover, the fields of pharmacology and medicinal psychiatry are significantly less predictable than detergent manufacture. It is often the case that the combination of two pharmaceutical agents will not have the same effect upon a patient as the effects of the two agents independently. Moreover, as is often the case, there will be detrimental side effects resulting from combining various pharmaceutical agents. The cited patents entirely fail to provide even a hint at what the likely effect might be if either agent, i.e., AMPT or Haloperidol, were combined and jointly administered with the other. There is no suggestion in the art that these agents could be combined. It is inappropriate to deny patent protection to a new pharmaceutical composition based upon a decision from the detergent arts.

Second, the decision in *Kerkhoven* was based upon the fact that there was no evidence of any unexpected advantages resulting from the claimed production methods. Specifically, in that decision, the Board explained, "appellant has failed to prove the superiority of his multi-slurry technique over the prior art's single-slurry technique for the production of detergent compositions."

In contrast, the present application describes the surprising and unexpected advantages of treatment schedules using AMPT and Haloperidol as compared to administering AMPT alone. See pages 9-11 and Case reports 16-19 on pages 32-36, in particular.

The Federal Circuit recently explained the importance of unexpected advantages in *In re Soni:*

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person or ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results."

54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995).

For at least these reasons, the present rejection under § 103 based upon the patents to Pozuelo and Pachter et al., must as a matter of law, be withdrawn.

C. The Rejection of Claims 9-15 Under § 103 Based Upon th '161 Pat nt to Pozuelo; the '635 Patent to Pachter et al., in View of U.S. Patents 5,789,411 to Gooberman et al. and 5,760,044 to Archer Must Be Withdrawn

In support of this ground of rejection, the Examiner contended:

> The present claims (e.g. claims 9-13 and 15) are directed to a method of treating narcotic addiction (e.g. addiction to heroin or cocaine or amphetamines or marijuana) by administering:
> I. alpha-methyl-para tyrosine (AMPT) and
> II. 4-[4-(p-chlorophenyl)-4-hydroxy-piperidino]-4'-fluorobuyrophenone (HALDOL or Haloperidol);
> and optionally further including NALTREXONE (e.g. claim 14).
>
> The combined Pozuelo and Pachter patent reference teaching (discussed above and hereby incorporated by reference in its entirety) differs from the presently claimed invention (e.g. claim 14) in failing to additionally administer NALTREXONE to treat narcotic addiction.
>
> However, the archer Patent teaches the administration of NALTREXONE or NALOXONE, separately, or in combination with a morphine derivative (e.g. see formula in abstract) to treat cocaine and amphetamine dependency. See e.g. Archer at col. 12; patent claims 18 and 20.
>
> Similarly, Gooberman et al. patent teach administering NALTREXONE for treating opioid (e.g. heroin) withdrawal. See e.g. col. 5 and Examples (e.g. example 1); patent claims 7, 9, 15, 23, 29).
>
> Accordingly, one of ordinary skill in the art at the time of applicant's invention would have been motivated to administer NALTREXONE along with AMPT and HALOPERIDOL in order to further treat narcotic addiction (e.g. to address narcotic withdrawal symptoms) in order to obtain the combined additive effect of each of the drugs taken separately.
>
> Courts have determined that it is indeed obvious to one of ordinary skill in the art to co-administer two (or more) pharmaceuticals, each of which is taught to have the same utility, when they are individually known to have that utility, absent unexpected results. See e.g. *In re Kerhoven*, 626 F.2d 846,205 USPQ 1069 (CCPA 1980).
>
> Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to additionally administer NALTREXONE along with AMPT and HALOPERIDOL for treating narcotic addiction as presently claimed.

Pages 5-6 of the December 13 Action.

This rejection is also improper and must be withdrawn. Claims 9-13 and 15 are directed to methods for treating certain addictions by administering AMPT and Haldol or Haloperidol. Claim 14 recites a method further in conjunction with treatment with Naltrexone.

It is unclear why the Examiner bases the rejection of claims 9-13 and 15 upon the previously discussed patents to Pozuelo and Pachter et al., and additionally upon the '411 patent to Gooberman et al. and the '044 patent to Archer. For the reasons previously expressed with regard to the rejection of claims 9-13 and 15, the patents to Pozuelo and Pachter et al. do not render the pending claims obvious.

Neither of the patents to Gooberman et al. nor Archer, provide any teaching or suggestion concerning the combinational use of AMPT with Haloperidol. Simply put, the patents to Gooberman et al. and Archer are not even relevant to the patentability of claims 9-13 and 15, and in no way, remedy the deficiencies of the patents to Pozuelo and Pachter et al.

As to claim 14, that claim recites a tri-agent combinational use of AMPT, Haloperidol, and Naltrexone. The Examiner correctly notes that Naltrexone is disclosed in both the patents to Gooberman et al. and Archer. However, neither of those patents provide any teaching or suggestion of using Naltrexone in combination with AMPT and Haloperidol.

Furthermore, if one followed the teachings of the patent to Gooberman et al. (as one must in relying upon that patent for the present rejection), then one would be instructed to utilize an anesthetic agent in combination with the Naltrexone. Claim 14 does not recite such combination. There is absolutely no teaching or suggestion in the patent to Gooberman et al. of using Naltrexone in combination with AMPT and Haloperidol.

Similarly, if one followed the teachings of the Archer patent, one would be motivated to administer Naltrexone with derivatives of 1,2,3,4,5,6-hexhydro-8-hydroxy-2,6-methano-3-benzazocines. That is, the Archer patent teaches away from the claims at issue. There is no mention or even a suggestion by Archer of administering Naltrexone with the combination of AMPT and Haloperidol.

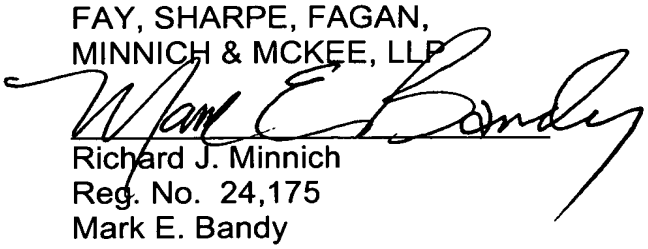
For at least these reasons, the rejection of claims 9-15 must be withdrawn.

D. Conclusion

In view of the foregoing, it is respectfully urged that all claims 9-15 are in condition for allowance.

Respectfully submitted,

FAY, SHARPE, FAGAN,
MINNICH & MCKEE, LLP



Richard J. Minnich
Reg. No. 24,175
Mark E. Bandy
Reg. No. 35,788
1100 Superior Avenue
Suite 700
Cleveland, Ohio 44114-2579
(216) 861-5582

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